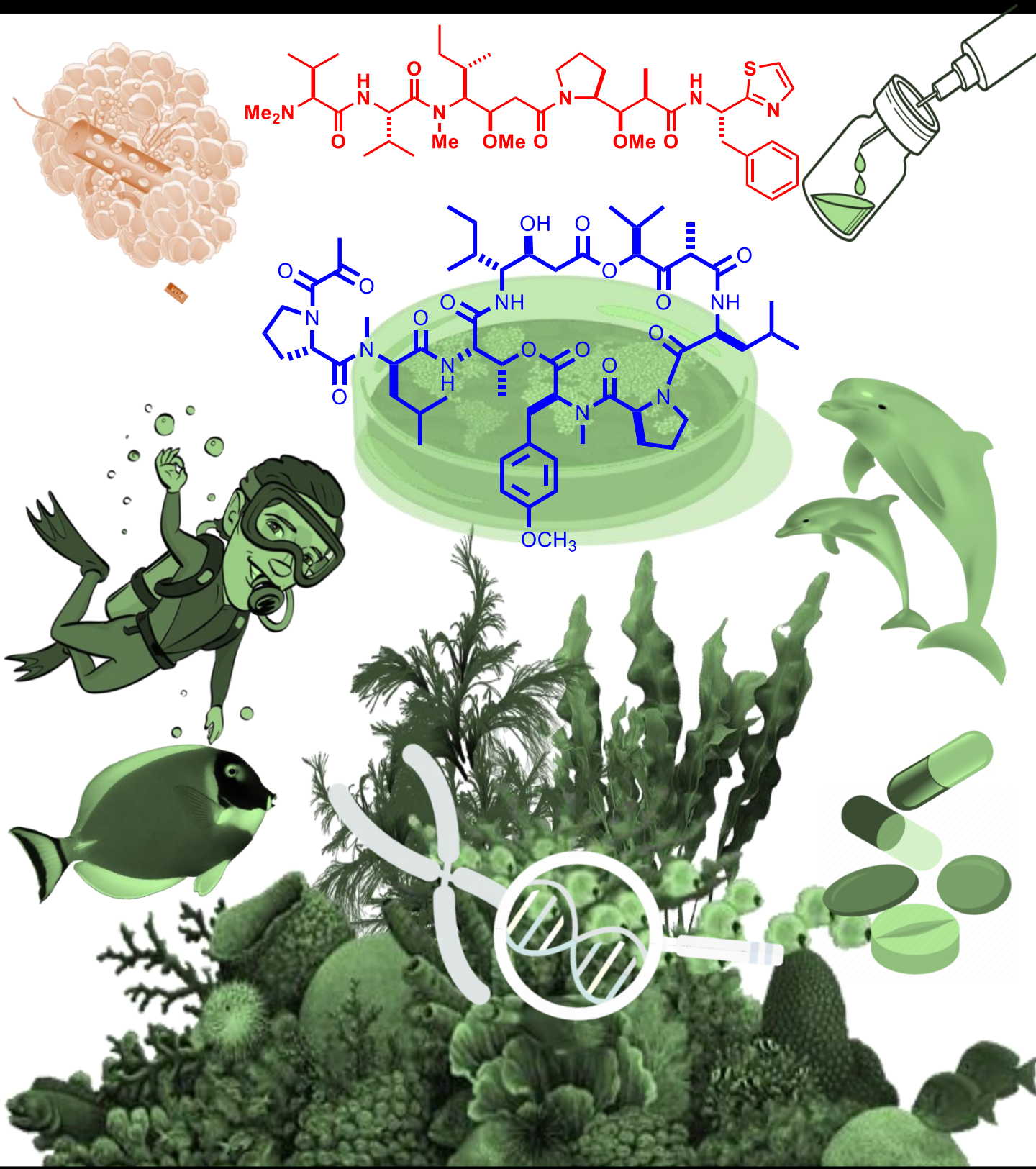
Marine Drugs

2021 – 2022 {Lecture 8}



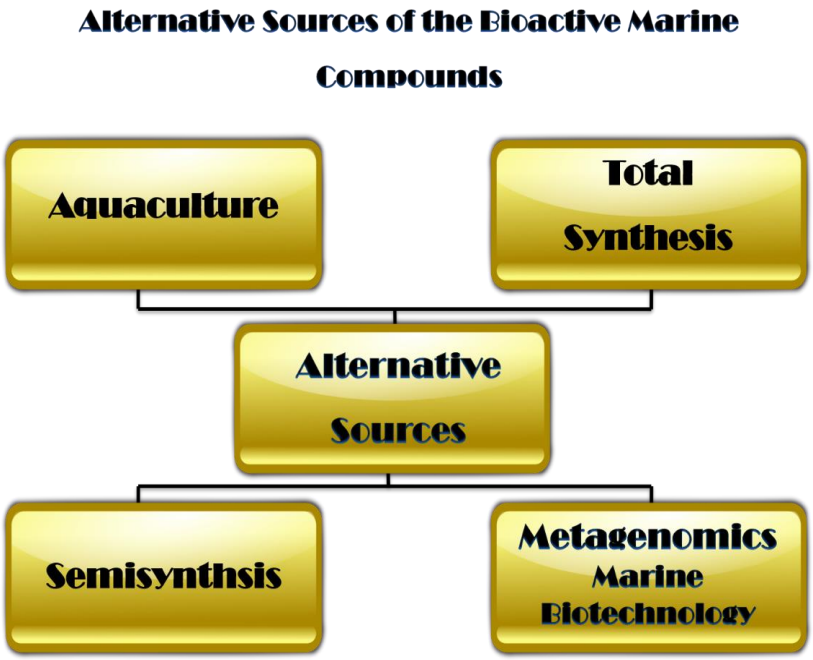
Dr. Omar M. Sabry

IV. Marine Biotechnology

Main Problems in Marine Drug Discovery

- Material supply is a main problem in marine drug discovery research. Marine organisms only produce low yields of bio-active compound.
- To obtain 1 gm of trabectedin, a drug for sarcomas, colorectal and ovarian cancer, approximately 1 ton of the tunicate should be extracted. A reliable source of material for drugs development is essential.
- Alternative solutions to overcome the problems are urgently needed. Alternative solutions to this problem.

Alternative Sources of the Rare Bioactive Marine Natural Compounds



1- Aquaculture for sustainable supplies of Marine-Derived Drugs Material.

Trabectedin {Yondelis®] was isolated from *Esteinascidia turbinata*. *Esteinascidia turbinata* is a tunicate normally lives in shallow waters Caribbean coastal. Trabectedin (Yondelis®) was reported to have a unique anti-cancer mechanism of action. It binds to the DNA and induces transcription inhibition.

Trabectedin (Yondelis®) was approved as anticancer drug by FDA in 2014. Working with structurally complex compounds where total or even semi synthesis is very difficult to be provided, aquaculture can be a solution. Aquaculture of *Esteinascidia turbinata*, is a success example of how aquaculture can be used to supply material for promising marine drugs candidate. Marine natural products isolated from tunicates, sponges or other marine invertebrate usually have a very complex structural complexity which are not feasible to be produced by total synthesis. Total synthesis of Trabectedin (Yondelis®) was completed but it is costly and needs 18 steps. However, it was not sufficient to be the only source for clinical development needs. PharmaMar, a pharmaceutical company developed Trabectedin decided to use natural sourcing as main material resource for pre-clinical and clinical needs. Finally, PharmaMar decided to switch the source of Trabectedin (Yondelis®) production from natural resources to semi-synthetic source as they isolated safracin B from a microorganism lives in symbiosis with the marine tunicate.

2- Chemical Synthesis of Marine-Derived Drugs (Ziconotide® - Prialt®)

Developing chemical synthesis is the main approach that currently used to produce marine-derived drugs candidates. One of case example of the success used of this approach is the chemical synthesis of ziconotide. The lead compound of ziconotide was ω- conotoxin which was isolated from cone snail. ω-conotoxin is a polypeptide consists of 27 amino acids. Chemical synthesis approach is feasible solution to be used, especially when working with less complex structure of compounds e.g. Cytarabine® and Ziconotide®.

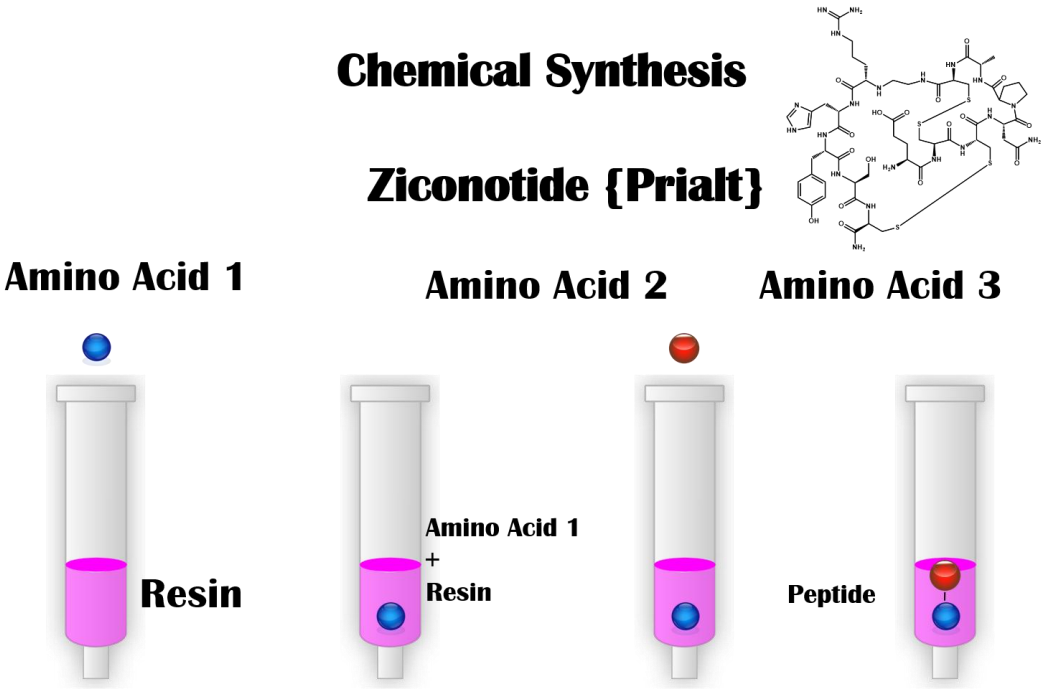
Eribulin is another example of totally synthetic marine drugs as:

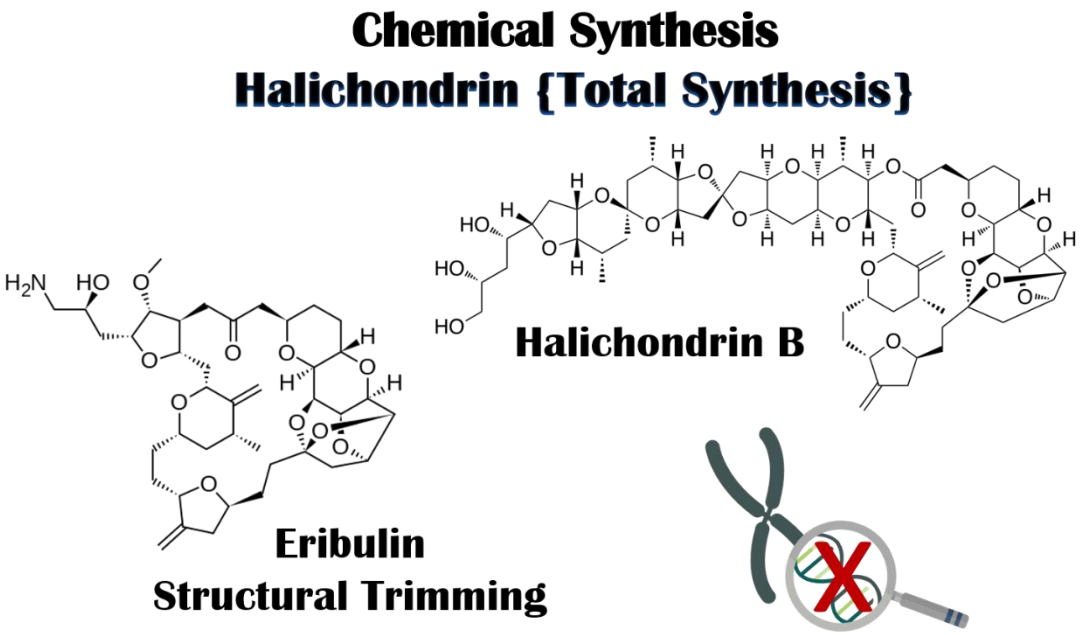
Aquaculture of *Halichondria* is an in-sufficient source for the Halichondrin B

Microbe(s) responsible for production of Halichondrin B couldn't be cultured

Gene cluster for biosynthesis of Halichondrin couldn't be isolated from the true

producers till now {Halichondrin B produced by the association between the different symbiont microorganisms}.

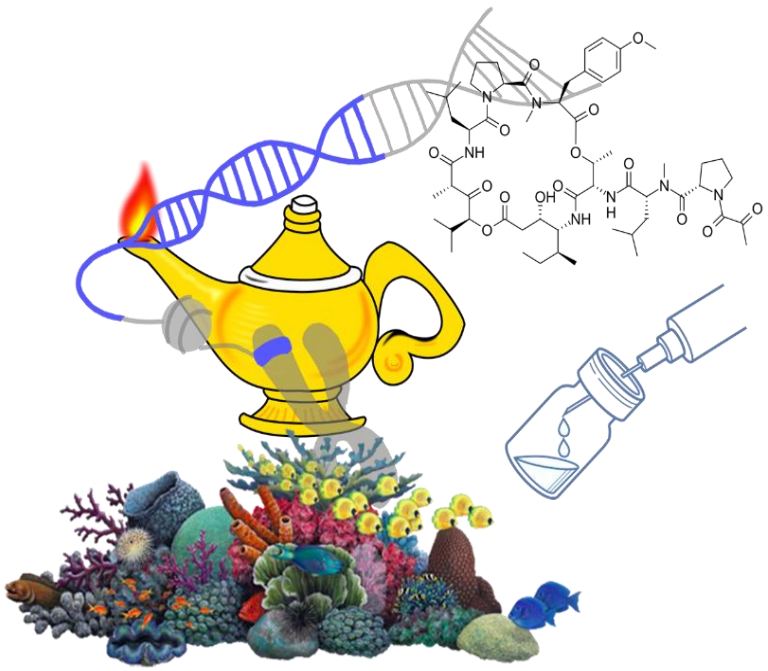




producers till now {Halichondrin B produced by the association between the different symbiont microorganisms}.

3- Biotechnology in Marine Drug Discovery

Compounds isolated from marine invertebrate were originating from endo-symbiotic microorganism. Numerous data showed that the bioactive compounds are produced either by the symbiont or by the association between the host and symbiont or by the association between the different symbiont microorganisms. Halichondrin B, a highly bioactive anti- mitotic macrolide {Tubulin assembly inhibitor} produced by associated microorganisms live in symbiosis with marine sponge *Halichondria okadai*. A new strategy of culture-independent method (Marine biotechnology) to explore the untapped reservoir of marine microbial chemical diversity has been developed. Metagenomics marine biotechnology is basically a modern genomics approach to isolate the DNA of microbial communities directly from their natural environments; therefore, difficulties associated with culturing the microbes can be avoided.



Since the genetic information that encoding the secondary metabolites produced by microorganism is typically clustered on the microorganisms' chromosomes, hence it is possible to predict the complete gene clusters of secondary metabolites biosynthesis on those organisms, which might provide a renewable source of the secondary metabolites. Once a gene has been identified, the genetic information can be used for compound production. Biotechnology can be simply defined as making other organisms work for us. Marine biotechnology is a rising area in Marine drug discovery. Marine Biotechnology is considered as the future work of marine natural products {marine drugs}. Marine Biotechnology includes Isolation of the gene cluster of the bioactive compound by isolation of the DNA and/or mRNA. Production of the bioactive compounds by using recombinant DNA technique. Production of new compounds with unique novel bioactivities by using mixed recombinant DNA.